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Cold fluids for induction of targeted temperature management: A sub-study of the TTH48 trial

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42

43 Conflicts of interest:

44 Markus Skrifvars reports having received a research grant from GE Healthcare, travel reimbursements and lecture fees
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46 as well as honorarium for consultancy from BD BARD, Benechill and Sedana Medical. Anders Grejs and Anni Jeppesen
47 reports having received lecture fees from Novartis. All other authors report that they have no conflicts of interest.

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70 **Abstract**

71 **Background**

72 Pre-intensive care unit (ICU) induction of targeted temperature management (TTM) with cold
73 intravenous (i.v.) fluids does not appear to improve outcomes after in out-of-hospital cardiac arrest
74 (OHCA). We hypothesized that this may be due to ineffective cooling and side effects.

75 **Methods**

76 A post hoc analysis of a sub-group of patients (n=352) in the TTH48 trial (NCT01689077) who
77 received or did not receive pre-ICU cooling using cold i.v. fluids. Data collection included patient
78 characteristics, cardiac arrest factors, cooling methods, side effects and continuous core
79 temperature measurements. The primary endpoint was the time to target temperature (TTT, <
80 34°C), and the secondary endpoints included the incidence of circulatory side effects, abnormal
81 electrolyte levels and hypoxia within the first 24 h of ICU care. A difference of 1 h in the TTT was
82 determined as clinically significant a priori.

83 **Results**

84 Of 352 patients included in the present analysis, 110 received pre-ICU cold fluids. The **median** time
85 to the return of spontaneous circulation (ROSC) and TTT in the pre-ICU cold fluids group was longer
86 than that of the group that did not receive pre-ICU cold fluids (**318 vs. 281 min, $p < 0.01$**). In a linear
87 regression model including the treatment centre, body mass index (BMI), chronic heart failure,
88 diabetes mellitus and time to ROSC, the use of pre-ICU cold i.v. fluids was not associated with a
89 shorter time to the target temperature (standardized beta coefficient: 0.06, 95% CI for B -49 and 16,
90 $p = 0.32$). According to the receipt or not of pre-ICU cold i.v. fluids, there was no difference in the
91 proportion of patients with hypoxia on ICU admission (1.8% vs. 3.3%, $p = 0.43$) or the proportion of
92 patients with electrolyte abnormalities (hyponatremia: 1.8% vs. 2.9% $p = 0.54$; hypokalaemia: 1.8%
93 vs. 4.5%, $p = 0.20$). Furthermore, there was no difference in hospital mortality between the groups.

94 **Conclusions**

95 The initiation of TTM with cold i.v. fluids before ICU arrival did not decrease the TTT. We detected
96 no significant between-group difference in mortality or the incidence of side effects according to
97 the administration or not of pre-ICU cold i.v fluids.

98 **Keywords:** Targeted temperature management; Pre-ICU cooling, Time to target temperature,
99 Intravenous cooling

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118 **Introduction**

119 Targeted temperature management (TTM) is commonly utilised in the treatment of out-of-hospital
120 cardiac arrest (OHCA) patients.^{1,2} The optimal mode and timing of induction are unclear.³ Although
121 several cooling methods are used in the intensive care unit (ICU), pre-ICU cooling is generally
122 performed using cold intravenous (i.v.) fluids, given the simplicity of the method. According to some
123 small studies, potential benefits associated with this pre-ICU cold i.v. fluids included a shorter time
124 to the target temperature (TTT).⁴⁻⁶ However, a previous study reported that the administration of
125 cold i.v. fluids prior to the time to return of spontaneous circulation (ROSC) led to increased side
126 effects.⁷ Some recent resuscitation guidelines have advised against the use of pre-ICU cold i.v.
127 fluids.⁸ In a large randomised controlled trial (RCT) on the use of pre-hospital cold fluids for TTM (*N*
128 = 1,000), Kim et al. found no clear survival benefit and an elevated risk of pulmonary oedema.⁴
129 Intuitively, rapid cooling after cardiac arrest should improve outcomes. However, it is not clear how
130 possible benefits and disadvantages of rapid cooling interact, resulting in mixed evidence on the
131 value of pre-ICU cold i.v. fluids.^{3,4,9-16} We hypothesized that the lack of a clear benefit may be due
132 to ineffective cooling or side effects of the cold pre-ICU i.v. fluids. If these side effects were better
133 understood, it might be possible to tailor treatments and ultimately use cold i.v. fluids as a cheap,
134 simple and applicable method to induce hypothermia before ICU admission.
135 In the present study, we aimed to determine the effects of pre-ICU cooling using cold i.v. fluids on
136 the TTT and incidence of side effects in a sub-group of patients treated with either standard or
137 prolonged TTM at 33°C included in the TTH48 trial.¹⁷

138 **Methods**

139 **Study population and setting**

140 We performed a post hoc analysis of a sub-group of patients in the TTH48 trial (NCT01689077) who
141 received or did not receive pre-ICU cooling using cold i.v. fluids. The original study compared TTM

142 at 33°C for 48 h versus 24 h in the ICU after OHCA. The protocol and statistical analysis of the TTH48
143 trial have been published previously.^{17,18} The original study included 355 unconscious OHCA patients
144 in 10 European ICUs who were randomized to TTM at 33°C for either 48 or 24 h. The inclusion criteria
145 were a Glasgow Coma Scale score of less than 8, aged between 18 and 80 y and ROSC sustainment
146 for more than 20 min prior to randomization. The exclusion criteria included terminal disease or a
147 do-not-resuscitate order, systolic blood pressure less than 80 mmHg, non-cardiac cause of cardiac
148 arrest, time to ROSC longer than 60 min, in-hospital cardiac arrest, severe coagulopathy, initial
149 rhythm asystole in an unwitnessed OHCA, time from cardiac arrest to initiation of cooling of > 240
150 min, neurological disease with cognitive impairment, persistent cardiogenic shock, an acute stroke
151 or intracerebral bleeding and acute coronary bypass surgery.

152 On the first hospital day, the patients were screened in the ICU and could be included until 23 h
153 from reaching the target temperature. In some patients, TTM was initiated before ICU arrival using
154 cold fluids, and the amount and type of fluid were recorded in the case report form (CRF). There
155 was no protocol for pre-ICU cold i.v. fluids administration (i.e. fluids were given as deemed
156 appropriate by the treating clinician). Core bladder, rectum or oesophagus temperatures were
157 measured using intravascular probes. Target temperature was maintained using either invasive or
158 surface cooling devices. After TTM was maintained at 33°C for the duration mandated by
159 randomization, rewarming was started at a rate of 0.5°C/h until a temperature of 37°C was reached.
160 In cases of severe adverse events, such as a recurring cardiac arrest, the treating clinician could
161 select to rewarm patients early at a rate of 0.5°C/h to 36°C.

162 **Endpoints**

163 The primary endpoint was the time from ROSC to reaching a target temperature of < 34°C. A
164 reduction of at least 1 h in the TTT was considered clinically significant. We created composite
165 endpoints to compare successful cooling and the global efficacy of cooling. Successful cooling was

defined as the time from ROSC to reaching the target temperature of less than 294 min (median). Globally effective cooling was defined as successful cooling without any of following: severe arrhythmia, considered pulseless ventricular tachycardia/ventricular fibrillation or unstable haemodynamics, despite treatment; a severe circulatory adverse event, defined as MAP of < 60 mmHg, despite comprehensive treatment; or hypoxia, defined as paO_2 of < 8 kPa. Other outcome endpoints included any occurrence of abnormal electrolyte levels or hypoxia during the first 24 h of ICU care, adverse events during the ICU stay and survival and neurological outcomes 6mo after hospital discharge. Survival status after 24, 48 and 72 h was recorded, in addition to seizures, circulatory hypotension, arrhythmias, gastrointestinal adverse events, renal replacement, pneumonia, infections, sepsis, bleeding and transfusions. We used the same definitions for adverse effects and a favourable neurological outcome (CPC1 or 2) as those applied in the original TTH48 study.¹⁷ In terms of electrolyte abnormalities, hypernatremia hyponatremia, hypokalaemia and hypochloraemia were classified as $\text{Na}^+ > 145 \text{ mmol/L}$, $\text{Na}^+ < 130 \text{ mmol/L}$, $\text{K}^+ < 3.0 \text{ mmol/L}$ and $\text{Cl}^- > 109 \text{ mmol/L}$, respectively. Any respiratory adverse event was considered hypoxia.

Statistical methods

The study population was divided into two groups according to whether pre-ICU cold i.v. fluids were administered. Categorical data are presented as **numbers of patients and percentages**. Continuous parameters were assessed for normality and presented either as means (standard deviation [SD]) or medians (interquartile range [IQR]). Categorical parameters were compared using a chi-square test. Continuous variables were compared using the Student's *T*-test or Mann–Whitney *U* test.

We performed a multivariate linear regression to determine the effects of pre-ICU cold i.v. fluid cooling on the time from ROSC to reaching the target temperature. We analysed baseline factors associated with successful cooling and performed univariate linear regression analysis on ROSC to target temperature time for baseline factors associated with successful cooling with $p < 0.20$. In the

190 multivariate linear regression analysis, factors with a p value of < 0.05 in the univariate analysis were
191 included. Factors included in the multivariate linear regression model were the use of pre-ICU cold
192 i.v. fluids, ROSC delay, treatment centre, previous heart failure, diabetes mellitus and body mass
193 index (BMI). Weight was excluded to avoid collinearity with BMI. The mean (SD) hourly
194 temperatures of each patient were calculated during the first 24 h and compared using a mixed
195 linear model with compound symmetry that included the interaction between cold fluid use with
196 time. In cases where data on mean hourly temperatures of a patient were missing, the patient was
197 excluded from the mean hour temperature analysis. All other patient-related measurements were
198 included in the model. Mortality and time to death were visualized using Kaplan–Meier curves, and
199 the mortality between groups was compared using a log rank test. A p value of < 0.05 was
200 considered significant. All analyses were conducted using IBM SPSS Statistics for Windows, Version
201 25.0. (IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2016 (Microsoft Corporation,
202 Redmond, Washington, USA)

203 **Results**

204 **Included patients**

205 Of the 355 patients included in the original trial, 352 were included in the present analysis, of which
206 110 received pre-ICU cold i.v. fluids. Exact cooling times were available for 345 patients, and these
207 data were included in the TTT analysis. The pre-ICU cold fluids administered included 500–3,000 ml
208 **(median 1000ml IQR 1000-2000 ml)** of 4°C saline, Ringer’s solution or another crystalloid solution,
209 such as salt solutions (e.g. saline) with small molecules.

210 **Baseline characteristics**

211 The baseline and resuscitation characteristics of the patients who received cold fluids and those
212 who did not were compared (Table 1). There were more patients with chronic heart failure (NYHA
213 class 4) in the group given pre-ICU cold fluids (11.8% vs. 2.1%, $p < 0.001$), as shown in Table 1. There

214 were no other significant between-group differences in the baseline characteristics of the patients,
215 including cardiac arrest- or resuscitation-related factors (Table 1).

216 **TTM-related factors**

217 Table 2 provides information on factors relating to the induction and maintenance of TTM. **The**
218 **mean (347 min vs. 268 min, $p = 0.01$) and median (318 min vs. 281 min, $p < 0.01$) times from ROSC**
219 **to reaching the target temperature increased significantly in the group given pre-ICU cold i.v.**
220 **fluids.** The most common cooling method in the ICU was invasive cooling using an intravascular
221 catheter ($n = 218$, 62%), with no significant between-group difference in the type of device used. All
222 the patients were cooled in the ICU using an intravascular catheter or some other device.

223 In the group given pre-ICU cold i.v. fluids, a higher number of patients received surface cooling as
224 compared with that in the group that did not receive this treatment (50% vs. 42%, $p = 0.02$).

225 **Correlation of pre-ICU fluid cooling and TTT**

226 Several factors were associated with more rapid cooling in the univariate analysis (Supplementary
227 online Table 1). Accordingly, several factors were related to the TTT in the linear regression analysis
228 (Table 3). In the univariate analysis, the use of pre-ICU cold i.v. fluids (standardized beta coefficient:
229 0.14, 95% CI for B 11 and 76, $p = 0.01$) was associated with a longer TTT. However, in a multiple
230 linear regression model that included significant factors (e.g. ROSC delay, treatment centre, heart
231 failure, diabetes mellitus, and BMI) associated with the TTT, the use of pre-ICU cold i.v. fluids was
232 not associated with any change in the TTT (standardized beta coefficient: 0.06, 95% CI for B -49 and
233 16, $p = 0.32$). In contrast, BMI (standardized beta coefficient: 0.29, 95% CI for B 6 and 12, $p < 0.01$)
234 and previous heart failure (standardized beta coefficient: 0.13, 95% CI for B 22 and 156, $p = 0.01$)
235 were associated with prolonged time from ROSC to target temperature. The linear regression model
236 results are presented in Table 3.

237 **Patients' temperatures in the ICU**

238 The mean patient temperatures for the first 24 h from ICU admission are shown in Figure 1. In a
239 mixed linear model, the use of pre-ICU cold fluids was associated with higher mean temperatures
240 for the first 24 h from ICU admission ($p = 0.003$), without any clear interaction with time. There was
241 no difference in the proportion of patients successfully cooled or the global effectiveness of cooling
242 between groups (Table 2).

243 **Adverse events and outcomes**

244 The occurrence of adverse events was not different in patients who did or did not receive pre-ICU
245 fluids (Table 4). There were no significant differences in mortality after 24, 48 or 72 h (Table 4). In
246 addition, there was no difference in the time to mortality or 180-d mortality ($p = 0.8$), as shown in
247 Figure 2. Furthermore, there was no significant between-group differences in favourable
248 neurological outcomes (CPC1 or 2) at discharge (3.9% absolute difference, $p = 0.46$) or 6 mo post-
249 discharge (0.6% absolute difference, $p = 0.78$).

250 **Discussion**

251 **Main findings**

252 We studied the effects of TTM induction using pre-ICU cold i.v. fluids on the TTT and side effects of
253 cold fluids in patients included in the randomized TTH48 trial, comparing 24 and 48 h of TTM at
254 33°C. Patients who received pre-ICU cold fluids did not have a shorter TTT than those who did not.
255 In addition, the body temperatures of the patients in the group that received cold fluids were higher
256 than those of the patients who did not, despite TTM induction during the first 24 h of admission.
257 We detected no between-group difference in side effects, such as electrolyte abnormalities or
258 hypoxia. In accordance with the findings of previous research,¹⁹ a high BMI was associated with a
259 prolonged TTT in the present study. The study design precludes conclusions about causality.
260 However, taken together, the findings do not support benefits of routine clinical use of cold
261 fluids in TTM in the pre-ICU setting. It may well be that early TTM may be achieved using more novel

262 methods, such as trans-nasal-evaporative cooling, which was recently shown to be feasible in the
263 pre-hospital setting.²⁰

264 Previous animal studies on TTM induction showed that faster induction of the target temperature
265 was beneficial.^{21,22} In patients, the evidence is mixed and furthermore, the efficacy of rapid cooling
266 is difficult to ascertain in patients with severe neurological injuries given the apparent ease of
267 cooling.^{3,4,12,14,23} Due to its simplicity, the use of cold fluids is appealing. However, Scales et al.
268 reported that pre-hospital cooling initiated 5 min after ROSC did not increase the likelihood of
269 achieving a target temperature of 32–34°C within 6 h of hospital arrival.²³ On the other hand, a
270 slightly older study by Larsson et al. pointed to the efficacy of TTM induction and maintenance with
271 cold and ice packs in the ICU.²⁴ In one of only a few large RCTs on TTM induction with cold fluids,
272 the authors showed that although the use of cold fluids in the ambulance initially decreased each
273 patient's temperature by almost 1°C, the effect had almost disappeared 1 h later.^{6,25} Our study not
274 only supports these findings but points to problems with temperature management during the
275 following 24 h in the ICU. The results of the present study may be due to the mode of cooling, with
276 cold fluids administered as part of a treatment protocol that favours non-invasive methods, which
277 have been shown to be less efficient than intra-vascular cooling.²⁶ However, as our adjusted model
278 included the TTM treatment, the aforementioned factor cannot completely account for the lack of
279 efficacy of pre-ICU cold i.v. fluids. Less aggressive initiation of ICU TTM by the treating team due to
280 a false sense of security may be an alternative explanation for the TTT not decreasing in the group
281 that received pre-ICU cold i.v. fluids. The infusion of cold fluid may also have resulted in some form
282 of rebound hyperthermia or shivering, which would require deeper sedation. We found no
283 difference in the initial use of sedation between the two groups. In some centres, the patients were
284 transferred directly to the cardiac angiography suite, which may have delayed ICU admission and
285 ICU cooling. In such cases, TTM may have been induced and maintained by the cold i.v. fluids. This

286 may have introduced bias, including the finding of a longer time to effective cooling in the group
287 given pre-ICU cold i.v. fluids. However, despite a numerically longer time from ROSC to ICU
288 admission in this group, this between-group difference in ROSC to ICU admission time was not
289 statistically significant.

290 We found no difference in outcomes, depending on whether the patients received or did not receive
291 cold fluids. Nie et al. analysed five RCTs and concluded that pre-hospital TTM induced by i.v. infusion
292 of ice-cold fluids did not improve survival to hospital discharge or neurological outcomes.¹⁴ The
293 results of the present study are in line with those in the field. In a large RCT conducted by Kim et al.,
294 the use of pre-hospital cold fluids also failed to improve outcomes. However, the study by Kim et al.
295 was criticized, as not all the included patients received TTM in an ICU, and the cold fluids were
296 administered for only a few minutes using a pressure bag.²⁷ In contrast, in the present study, all the
297 patients were admitted to an ICU for either 24 or 48 h of TTM.

298 Potential side effects of cold fluids may also explain the lack of benefit of cold fluids in terms of
299 survival. However, in the present study, there were no increases in severe electrolyte disturbances,
300 adverse haemodynamics or hypoxia. Hypoxia may develop due to fluid overload, , especially when
301 large volumes of cold fluids are administered. Jacobshagen et al. reported that pulmonary function
302 worsened when inducing TTM with cold fluid.²⁸

303 **Acknowledgements**

304 The current study has several strengths. The patients were from a large multicentre RCT, with
305 variables collected in a prospective manner, which increases the generalizability of our results. In
306 addition, the temperature data at ICU was extensive, and side effects were documented for at least
307 96 hours after ICU admission.

308 We acknowledge some limitations. The use of cold fluids overall and the volume and infusion rates
309 used, were as per the treating clinicians. Therefore our study precludes conclusion on causality. In

310 addition, we did not have exact data on the surface-cooling pad size or incidence of shivering and
311 our patient quantity was limited. Furthermore, we did not have a mandatory sedation or shivering
312 protocol. Finally, the post hoc setting limits the generalization of the results.

313 **Conclusions**

314 In the current study, the initiation of TTM before ICU arrival using cold i.v. fluids was not associated
315 with a decrease in the time required to reach a target temperature of $< 34^{\circ}\text{C}$. Furthermore, patients
316 who received cold fluids had slightly higher temperatures during the first 24 h as compared with
317 those who did not receive cold fluids. We did not find any association between cold fluid use and
318 electrolyte abnormalities, circulatory adverse effects, or outcomes.

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433 **Table 1.** Demographic characteristics and type of resuscitation.

Variable	Pre-ICU cold i.v. fluids given <i>n</i> = 110	Pre-ICU cold i.v. fluids not given <i>n</i> = 242	<i>P</i> value
Age (y), median (IQR)	62 (54 to 69)	62 (53 to 69)	0.97
Male sex, No. of patients (%)	86 (78)	207 (86)	0.09
Weight (kg), median (IQR) ^a	87 (76 to 97)	83 (75 to 92)	0.11
Neurological function pre-arrest, No. of patients (%)			
Normal (CPC 1)	108 (98)	234 (97)	0.44
Some disability (CPC 2)	2 (2)	8 (3)	
Medical history, No. of patients (%)			
Previous myocardial infarction	18 (16)	36 (15)	0.75
Previous PCI or CABG	15 (14)	40 (17)	0.48
Previous cardiac arrest	1 (1)	2 (1)	0.94
Chronic heart failure (NYHA IV)	13 (12)	5 (2)	<0.01
Chronic obstructive pulmonary disease	7 (6)	17 (7)	0.82
Liver cirrhosis	0 (0)	3 (1)	0.25
Chronic renal failure with dialysis	1 (0.9)	1 (0.4)	0.57
Diabetes mellitus	17 (16)	46 (19)	0.44
Immunosuppression	1 (1)	2 (1)	0.94

Cardiac arrest location, No. of patients (%)			
Home	62 (56)	130 (54)	0.37
Public place	38 (35)	98 (41)	
Other out-of-hospital	10 (9)	14 (6)	
Arrest witnessed, No. of patients (%)			
Bystander	95 (86)	206 (85)	0.29
Emergency medical services	9 (8)	5 (13)	
Unwitnessed	6 (6)	23 (10)	
Type of resuscitation, No. of patients (%)			
Bystander-initiated CPR	86 (78)	207 (86)	0.09
Shockable rhythm	94 (86)	218 (90)	0.20
Defibrillation with AED	19 (17)	61 (25)	0.05
Mechanical chest compression	23 (21)	67 (28)	0.16
Intubation	109 (99)	228 (95)	0.05
Prehospital treatment			
Epinephrine (yes), No. of patients (%)	66 (60)	155 (64)	0.47
Amiodarone (yes), No. of patients (%)	40 (36)	105 (43)	0.21
Time to ROSC (min), mean (SD) ^b	21 (11.5)	25 (20.1)	0.06

^aData missing for one patient. In some cases, the patient's weight was estimated and not measured. ^bData missing for three patients.

Acronym key: IQR= interquartile range, SD= standard deviation, CPC= cerebral performance category, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, NYHA=New York Heart Association classification, CPR= cardiopulmonary resuscitation, AED= automated external defibrillator, ROSC= return of spontaneous circulation

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Table 2. Cooling-related factors.

Variable	Pre-ICU cold i.v. fluids given <i>n</i> =110	Pre-ICU cold i.v. fluids not given <i>n</i> = 242	<i>P</i> value
Time from ROSC to ICU admission (min) Median (IQR) ^a	135 (86 to 191)	125 (76 to 170)	0.11
Time from ROSC to TT (min) Median (IQR) ^b	318 (245 to 418)	281 (214 to 367)	<0.01
Amount of cold pre-ICU fluids given No. of patients (%) ^c			
500ml	3(4)		
1000ml	37(49)		
1500ml	8(11)		
2000ml	21(28)		
2500ml	3(4)		
3000ml	3(4)		
Successful cooling ^d No. of patients (%)	47 (43)	125 (52)	0.14
Globally effective cooling, No. of patients (%)	36 (33)	97 (40)	0.20

Pre-ICU and pre-hospital cooling, No. of patients (%)			
Pre-hospital	43 (39)	21 (9)	<0.001
In hospital (pre-ICU)	59 (54)	12 (5)	
Both	8 (7)	4 (2)	
Cooling methods in the ICU, No. of patients (%)			
Surface cooling	60 (50)	97 (42)	0.02
Invasive cooling	67 (61)	151 (62)	0.79
Diuresis until TT, median (IQR)	368 (180 to 593)	330 (176 to 581)	0.20
Sedation administered ^f	109 (99)	235 (97)	0.34
Opioids administered ^g	86 (78)	167 (69)	0.08
Core temperature Measurement location, ^h No. of patients (%)			
Bladder	74 (90)	103 (81)	0.06
Nasopharynx	8 (10)	25 (20)	
Temperature 72 h after time 0, mean (SD)	37.4 (0.59)	37.3 (0.85)	0.12

454 ^aData missing for 7 patients, ^bdata missing for 12 patients, ^cdata missing for 35 patients, ^ddata missing for 7 patients,

455 ^edata missing for 8 patients, ^fpropofol or midazolam, ^gfentanyl or remifentanyl, and ^hdata missing for 142 patients.

456 Acronym key: IQR= interquartile range, SD= standard deviation, ICU= intensive care unit, ROSC= return of spontaneous

457 circulation TT= target temperature

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459 **Table 3.** Multiple linear regression of factors associated with the TTT.

Independent variable	Standardized beta coefficients	P	Standardized beta coefficients	P
	in univariate analysis (95% CIs for B)	value	in multivariate analysis (95% CIs for B)	value
Weight	0.32 (2.0 and 3.8)	<0.01		
BMI	0.32 (6.9 and 13)	<0.01	0.29 (6 and 12)	<0.01
Previous AMI	-0.08 (-72 and 11)	0.15		
Chronic obstructive pulmonary disease	0.06 (-27 and 95)	0.27		
Liver cirrhosis	0.06 (-70 and 260)	0.26		
Previous heart failure NYHA classification 4	0.18 (43 and 180)	<0.01	0.13 (22 and 156)	0.01
Diabetes mellitus	-0.12 (-83 and -3.7)	0.03	-0.09 (-71 and 7.5)	0.11
ROSC delay (min)	-0.12 (-1.8 and -0.13)	0.02	-0.07 (-2.0 and 0.42)	0.20
Pre-ICU cold i.v. fluid treatment	0.14 (11 and 76)	0.01	0.06 (-49 and 16)	0.32
Cardiac arrest to ICU admission time (min)	0.06 (-0.001 and 0.004)	0.24		
Hospital/site	-0.11 (-1.1 and -0.02)	0.04	-0.07 (-0.94 and 0.15)	0.16

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461 Acronym key: BMI= body mass index, AMI= acute myocardial ICU= intensive care unit, ROSC= return of spontaneous
462 circulation, TTT= time to target temperature

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469 **Table 4.** Adverse events and patient outcomes.

Variable	Pre-ICU cold i.v. fluids given <i>n</i> = 110	Pre-ICU cold i.v. fluids not given <i>n</i> = 242	<i>P</i> value
Seizure, No. of patients (%)			
Local	13 (12)	32 (13)	0.74
Global	16 (15)	48 (20)	0.23
Circulation, No. of patients (%)			
Mild	46 (42)	67 (28)	0.08
Moderate	14 (13)	39 (16)	
Severe	6 (6)	9 (4)	
Circulatory failure	4 (4)	9 (4)	
Mild arrhythmia	25 (22)	45 (19)	0.26
Moderate arrhythmia	16 (15)	29 (12)	
Severe arrhythmia	13 (12)	27 (11)	
Pacing	7 (6)	12 (5)	0.59
Pulmonary, No. of patients (%)			
Hypoxia (paO ₂ < 8 kPa)	2 (2)	8 (3)	0.43
Pneumonia	48 (44)	114 (47)	0.54
Gastrointestinal, No. of patients (%)			
Mild	7 (6)	14 (6)	0.37
Moderate	6 (6)	5 (2)	
Severe	3 (3)	9 (4)	
Renal, No. of patients (%)			
Renal replacement therapy	8 (7)	19 (8)	0.85
Infection, No. of patients (%)	40 (36)	89 (37)	0.92
Patient outcomes			
Died, No. of patients (%)			

Within 24 h	1 (0.9)	1(0.4)	0.57
Within 48 h	2 (2)	4 (2)	0.91
Within 72 h	3 (3)	9 (4)	0.63
In hospital	26 (24)	58 (24)	0.94
CPC1 or 2 at ICU discharge, No. of patients (%)	62 (56)	127 (53)	0.46
GCS score at ICU discharge, ^a No. of patients (%)			
3–8	8 (7)	15 (6)	0.58
9–12	2 (2)	7 (3)	
Died within 6 mo, No. of patients (%)	34 (31)	74 (31)	0.95
CPC1 or 2 at 6 mo, No. of patients (%)	72 (66)	160 (66)	0.78
Length of hospital stay (d), median (IQR)	12 (7 to 20)	11 (6 to 19)	0.31
Survivors	14(11)	13 (11)	0.93
Non-survivors	5(7)	5(5)	0.22

^aData missing for two patients.

Acronym key: IQR= interquartile range, SD= standard deviation, ICU= intensive care unit, ROSC= return of spontaneous circulation, CPC= cerebral performance category, GCS= Glasgow coma scale,

Supplementary online Table 1. Factors associated with successful cooling.

Variable	Successful cooling (ROSC to TT< 294 min) <i>n</i> = 173	Unsuccessful cooling (ROSC to TT> 294 min) <i>n</i> = 172	<i>P</i> value
Age (y), median (IQR)	61,5 (53 to 69)	62 (54 to 69)	0.89
Male sex, No. of patients (%)	145 (83)	142 (83)	0.76
Weight ^a (kg), median (IQR)	80 (75 to 90)	90 (80 to 100)	<0.01
BMI, median (IQR)	25.3 (23.8 to 27.8)	27.7 (24.8 to 30.8)	<0.01
Neurological function pre-arrest, No. of patients (%)			0.20
Normal (CPC1)	170 (98)	165 (96)	
Some disability (CPC2)	3 (2)	7 (4)	
Medical history, No. of patients (%)			

Previous myocardial infarction	26 (15)	28 (16)	0.70
Previous PCI or CABG	25 (14)	30 (17)	0.43
Previous cardiac arrest	0 (0)	3 (2)	0.08
Chronic heart failure (NYHA IV)	4 (2)	14 (8)	0.02
Chronic obstructive pulmonary disease	15 (9)	8 (5)	0.14
Liver cirrhosis	3 (2)	0 (0)	0.08
Chronic renal failure with dialysis	1 (1)	1 (1)	0.99
Diabetes mellitus	26 (15)	37 (22)	0.11
Immunosuppression	1 (1)	2 (1)	0.56
Cardiac arrest location, No. of patients (%)			
Home	93 (54)	94 (55)	0.88
Public place	69 (40)	65 (38)	
Other out-of-hospital	11 (6)	10 (6)	
Arrest witnessed, No. of patients (%)			
Bystander	148 (86)	147 (85)	0.52
Emergency medical services	13 (8)	9 (5)	
Unwitnessed	12 (7)	16 (9)	
Type of resuscitation, No. of patients (%)			
Bystander-initiated CPR	144 (83)	144 (84)	0.90
Shockable rhythm	153 (88)	154 (88)	0.98
Defibrillation with AED	33 (19)	46 (27)	0.49
Mechanical chest compression used	48 (28)	41 (24)	0.48
Intubation	167 (97)	164 (95)	0.58
Pre-hospital treatment, No. of patients (%)			
Pre-ICU cold i.v. fluid bolus	48 (28)	59 (34)	0.19
Pre-ICU cold i.v. fluid amount (ml) median (IQR)	1500 (1000 to 2000)	1000 (1000 to 2000)	0.56
Epinephrine	110 (64)	109 (63)	0.97
Amiodarone	73 (42)	70 (40)	0.78

475 ^aData missing for one patient. In some cases, the patient's weight was estimated and not measured.

476 Acronym key: IQR= interquartile range, SD= standard deviation, CPC= cerebral performance category, PCI=

477 percutaneous coronary intervention, CABG= coronary artery bypass graft, NYHA=New York Heart Association

478 classification, CPR= cardiopulmonary resuscitation, AED= automated external defibrillator, ROSC= return of
 479 spontaneous circulation, TT= target temperature

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481 **Supplementary online Table 2.** ICU admission outcomes.

Variable	Pre-ICU cold i.v. fluids given <i>n</i> = 110	Pre-ICU cold i.v. fluids not given <i>n</i> = 242	<i>P</i> value
FiO ₂ ^a , median (IQR)	60 (50 to 60)	51 (41 to 60)	0.44
PaO ₂ ^b , median (IQR)	15 (11 to 22)	16 (12 to 23)	0.79
Saturation ^c , median (IQR)	97 (92 to 99)	98 (91 to 99)	0.23
Hyponatremia, ^d No. of patients (%)	2 (2)	7 (3)	0.54
Hypernatremia, ^e No. of patients (%)	0 (0)	4 (2)	0.17
Na, median (IQR)	139 (136 to 140)	138 (136 to 140)	0.32
Hypokalaemia, ^e No. of patients (%)	2 (2)	11 (5)	0.20
K, median (IQR)	4 (3 to 4)	4 (4 to 5)	0.11
Hypochloraemia, ^f No. of patients (%)	25 (23)	59 (24)	0.80
Cl, Median (IQR)	107 (104 to 110)	107 (104 to 110)	0.90
Na, K or Cl abnormality ^h No. of patients (%)	28 (25)	79 (33)	0.21

482 ^aData missing for 8 patients, ^bdata missing for 2 patients, ^cdata missing for 36 patients, ^ddata missing for 7 patients,
 483 ^edata missing for 6 patients, ^fdata missing for 57 patients, ^gdata missing for 7 patients, and ^hdata missing for 52
 484 patients.

485 Acronym key: IQR= interquartile range, FiO₂= Fraction of inspired oxygen, PaO₂= partial pressure of oxygen

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